REMARKS

Applicants submit the foregoing amendments and following remarks in response to the Office Action dated September 6, 2005. Claims 46 and 48 have been cancelled. Claims 42-44, 47, and 52-53 have been amended to remove reference to a signal peptide. Applicants submit that no new matter was added by the amendments, and that support for the amendments can be found throughout the specification. Claims 42-45, 47 and 49-55 remain present for further examination.

Applicants thank the Examiner for his review of the instant application, and request reconsideration of the application in view of the following remarks.

Amendments to the Specification

The specification was objected to for containing embedded hyperlinks and/or browser-executable code. Applicants have amended the specification to remove browser-executable code.

Rejection under 35 U.S.C. §101 – Utility

The PTO rejects the pending claims under 35 U.S.C. § 101 as lacking patentable utility. The PTO alleges that the invention is not supported by either a substantial asserted utility or a well-established utility.

The PTO states that the data set forth in the specification are preliminary at best because the specification does not teach the expression of the PRO180 polypeptide nor any particular biological activity or function of the polypeptide. The PTO cites Hu et al. for support of its position that the literature cautions against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. The PTO relies on Chen et al. in support of its position that one of skill in the art would not find that that there is a general correlation between changes in mRNA level and changes in protein level. The PTO also relies on Haynes *et al.*, Gygi *et al.* and Hanish in further support and states that declarations and supporting references submitted with Applicants' previous responses are insufficient to overcome the rejection.

Applicants respectfully traverse.

Utility – Legal Standard

Applicants begin by again setting forth the legal standard by which utility is to be determined. According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid or polypeptide is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added).

In addition, the mere consideration that further experimentation might be performed to more fully develop the claimed subject matter does not support a finding of lack of utility. M.P.E.P. § 2107.01 III cites *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) in stating that "Usefulness in patent law ... necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." Further, "[T]o violate § 101 the claimed device must be totally incapable of achieving a useful result" *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999), *citing Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed.Cir.1992).

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1), gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular

practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, in assessing the credibility of the asserted utility, the M.P.E.P. states that "to overcome the presumption of truth that an assertion of utility by the applicant enjoys" the PTO must establish that it is "more likely than not that one of ordinary skill in the art would doubt (i.e., "question") the truth of the statement of utility." M.P.E.P. § 2107.02 III A. The M.P.E.P. cautions that:

> Rejections under 35 U.S.C. 101 have been **rarely sustained** by federal courts. Generally speaking, **in these rare cases**, the 35 U.S.C. 101 rejection was sustained either because the **applicant ... asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art.** M.P.E.P. § 2107.02 III B. (underline emphasis in original, bold emphasis added); citing *In re Gazave*, 379 F.2d 973, 978, 154 USPQ 92, 96 (CCPA 1967).

Utility need NOT be Proved to a Statistical Certainty – a Reasonable Correlation between the Evidence and the Asserted Utility is Sufficient

As previously noted, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). As Applicant's have previously pointed out, this is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty.** Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted

> utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

Applicants rely on *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) and *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985), which hold that the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true.** The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Applicant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence such that it is more likely than not those skilled in the art, to a reasonable probability, would believe that the claimed invention is useful as a diagnostic tool for cancer.

Substantial Utility

Summary of Applicants' Arguments and the PTO's Response

In an attempt to clarify Applicants' argument, Applicants offer a summary of their argument and the disputed issues involved. Applicants assert that the claimed polypeptides have utility as diagnostic tools for cancer, particularly rectal and lung cancer. Applicants are not asserting that the claimed polypeptides necessarily provide a definitive diagnosis of cancer, but rather that they are useful, alone or in combination with other diagnostic tools, to assist in the diagnosis of certain cancers. Applicants' asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO180 polypeptide is differentially expressed in rectal and lung tumors;

2. Applicants assert that it is well-established in the art that a change in the level of mRNA for a particular protein, e.g. an increase, generally leads to a corresponding change in the level of the encoded protein, e.g. an increase;

3. Given Applicants' evidence that the level of mRNA for the PRO180 polypeptide is increased in rectal tumor compared to normal rectal tissue, and in normal lung tissue compared to lung tumor, it is more likely than not that the PRO180 polypeptide is also differentially expressed in rectal and lung tumor. Polypeptides such as PRO180 that are differentially expressed in certain cancers are useful as diagnostic tools to distinguish tumor from normal tissue.

Applicants understand the PTO to be making several arguments in response to Applicants' asserted utility:

1. The PTO states that while the evidence reported in Example 18 shows differential expression of the nucleic acid, there is no data that the polypeptide is also differentially expressed;

2. The PTO cites Hu *et al.* to support its assertion that the literature cautions against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue; and

3. The PTO cites Haynes *et al.*, Chen *et al.*, Hanish and Gygi *et al.* for the proposition that gene expression and protein expression do not always correlate and thus the art is unpredictable; there is no clear "reasonable" correlation between gene expression and protein production.

As detailed below, Applicants submit that the PTO has failed to demonstrate that this is one of the "rare cases" where the applicants have "asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art." *M.P.E.P.* § 2107.02 III B. First, Applicants have submitted the declaration of J. Christopher Grimaldi, which establishes the reliability of the data of Example 18, and have provided sufficient evidence to establish the existence of a reasonable correlation between gene expression and protein expression. Second, the references provided by the PTO are not contrary to Applicants' arguments and evidence, and therefore do not support the PTO's position. Third, even if the PTO has met its initial burden,

Applicants have submitted enough rebuttal evidence such that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true. As stated above, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute or statistical certainty.** Given the evidence provided by Applicants, those of ordinary skill in the art, would be convinced, **to a reasonable probability**, that the asserted utility is true.

Applicants have established that the Gene Encoding the PRO180 Polypeptide is Differentially Expressed in Certain Cancers compared to Normal Tissue

Applicants submit that the gene expression data provided in Example 18 of the present application are sufficient to establish a specific and substantial utility for the claimed polypeptides related to the gene encoding the PRO180 polypeptide.

Applicants first turn to the PTO's arguments based on Hu *et al.* (J. Proteome Res., 2(4):405-12 (2003)) that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. *See Office Action* at 4.

In Hu, the researchers used an automated literature-mining tool to summarize and estimate the relative strengths of all human gene-disease relationships published on Medline. They then generated a microarray expression dataset comparing breast cancer and normal breast tissue. Using their data-mining tool, they looked for a correlation between the strength of the literature association between the gene and breast cancer, and the magnitude of the difference in expression level. They report that for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a *known* role in the disease. *See* Hu at 411. However, among genes with a 10-fold or more change in expression level, there was a strong correlation between expression level and a *published* role in the disease. *Id.* at 412. Importantly, Hu reports that the observed correlation was only found among estrogen receptor-positive tumors, not ER-negative tumors. *Id.*

The general findings of Hu are not surprising – one would expect that genes with the greatest change in expression in a disease would be the first targets of research, and therefore have the strongest known relationship to the disease as measured by the number of publications reporting a connection with the disease. The correlation reported in Hu only indicates that the

greater the change in expression level, the more likely it is that there is a *published* or *known* role for the gene in the disease, as found by their automated literature-mining software. Thus, Hu's results merely reflect a bias in the literature toward studying the most prominent targets, and reflect nothing regarding the ability of a gene that is 2-fold or more differentially expressed in tumors to serve as a disease marker.

Hu acknowledges the shortcomings of this method in explaining the disparity in Hu's findings for ER-negative versus ER-positive tumors: Hu attributes the "bias in the literature" toward the more prevalent ER-positive tumors as the explanation for the lack of any correlation between number of publications and gene expression levels in less-prevalent (and, therefore, less studied) ER-negative tumors. *Id.* Because of this intrinsic bias, Hu's methodology is unlikely to ever note a correlation of a disease with less differentially-expressed genes and their corresponding proteins, regardless of whether or not an actual relationship between the disease and less differentially-expressed genes exists. Accordingly, Hu's methodology yields results that provide little or no information regarding biological significance of genes with less than 5-fold expression change in disease. Nowhere in Hu does it say that a lack of correlation in their study means that genes with a less than five-fold change in level of expression in cancer cannot serve as a molecular marker of cancer.

Applicants note that they are not relying on any "role" that PRO180 has in cancer for their asserted utility. Instead, Applicants are relying on the differential expression of PRO180 in certain tumors compared to their normal tissue counterparts. Nowhere in Hu does it say that a lack of correlation in their study means that genes with a less than five-fold change in level of expression in cancer cannot serve as a molecular marker of cancer.

A lack of known role for the PRO180 gene in cancer does not prevent its use as a diagnostic tool for cancer. There is a difference between use of a gene for distinguishing between tumor and normal tissue on the one hand, and establishing a role for the gene in cancer on the other. Genes with lower levels of change in expression may or may not be the most important genes in causing the disease, but the genes can still show a consistent and measurable change in expression. While such genes may or may not be good targets for further research, they can nonetheless be used as diagnostic tools. Thus, Hu does not refute the Applicants' assertion that the PRO180 gene can be used as a cancer diagnostic tool because it is differentially expressed in certain tumors, and the PTO's response does not address Applicants' arguments.

In addition, the PTO's own written policies recognize that the utility of a nucleic acid does not depend on the function of the encoded gene product. The Utility Examination Guidelines published on January 5, 2001 state: "the utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have a specific and substantial utility because, e.g. it hybridizes near a disease-associated gene or it has a gene regulating activity." (Federal Register, Volume 66, page 1095, Comment 14); *see also Exhibits 1-3* attached hereto (U.S. Patent Nos. 6,465,185, 6,228,582, and 6,162,604) (patents on polymorphisms which are indicative of a predisposition to a particular condition are patentable even though they may or may not cause the disease itself). Similarly, here the disclosed nucleic acids, as well as the encoded polypeptides and related antibodies, are useful for determining whether an individual has cancer regardless of whether or not they are the cause of the cancer.

The position of the PTO requiring a known role for PRO180 in cancer for utility is also inconsistent with the analogous standard for therapeutic utility of a compound where "the mere identification of a pharmacological activity of a compound that is relevant to an asserted pharmacological use provides an 'immediate benefit to the public' and thus satisfies the utility requirement." M.P.E.P. §2701.01 (emphasis original). Here, the mere identification of altered expression in tumors is relevant to diagnosis of tumors, and, therefore, provides an immediate benefit to the public.

The PTO asserts that the first Grimaldi declaration states that Example 18 showed mRNA expression but does not state that the protein was expressed. As previously noted, the data in Example 18 demonstrates that the mRNA encoding PRO180 is differentially expressed in rectal and lung tumors. In paragraphs 6 and 7 of his declaration, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or underexpressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. He also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal." He explains that, "The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." (first Grimaldi Declaration, Paragraph 7).

As Mr. Grimaldi states, "[i]f a difference is detected, this indicates that *the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes*, to screen samples to differentiate between normal and tumor." (first Grimaldi Declaration, Paragraph 7, emphasis added). The data presented in Example 18 show that the gene encoding PRO180 is differentially expressed in rectal and lung tumors, and the first Grimaldi declaration confirms that the disclosed gene and its corresponding polypeptide and antibodies are useful as diagnostic tools.

Applicants submit that the declaration is based on personal knowledge of the relevant facts at issue. Mr. Grimaldi is an expert in the field and conducted or supervised the experiments at issue. Applicants remind the PTO that "[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned." PTO Utility Examination Guidelines (2001) (emphasis added). In addition, declarations relating to issues of fact should not be summarily dismissed as "opinions" without an adequate explanation of how the declaration fails to rebut the Examiner's position. *In re Alton* 76 F.3d 1168 (Fed. Cir. 1996). As discussed herein, the PTO has not supplied any reasons or evidence to question the accuracy of the facts upon which Mr. Grimaldi based his opinion. Mr. Grimaldi has personal knowledge of the relevant facts, has based his opinion on those facts, and the PTO has offered no reason or evidence to reject either the underlying facts or his opinion. Therefore, the PTO should accept the statements in Mr. Grimaldi's Declaration.

In conclusion, Applicants submit that the evidence reported in Example 18, combined with the first Grimaldi Declaration previously submitted, establish that there is at least a two-fold difference in PRO180 cDNA between rectal and lung tumor tissue compared to normal rectal and lung tissue. Therefore, it follows that expression levels of the PRO180 gene can be used to distinguish rectal and lung tumor tissue from normal rectal and lung tissue.

As Applicants explain below, it is more likely than not that the PRO180 polypeptide can also be used to distinguish lung and rectal tumor tissue from normal lung and rectal tissue.

Applicants have established that the Accepted Understanding in the Art is that there is a Positive Correlation between mRNA Levels and the Level of Expression of the Encoded Protein

Applicants next turn to the second portion of their argument in support of their asserted utility – that it is well-established in the art that a **change** in the level of mRNA for a particular

protein, generally leads to a corresponding **change** in the level of the encoded protein; given Applicants' evidence of differential expression of the mRNA for the PRO180 polypeptide in rectal and lung tumor, it is likely that the PRO180 polypeptide is differentially expressed; and proteins differentially expressed in certain tumors have utility as diagnostic tools.

In response to Applicants' assertion, the PTO cites Haynes *et al.* (Electrophoresis, 19(11):1862-71 (1998)), Chen *et al.* (Mol. and Cell. Proteomics, 1:304-313 (2002)), Gygi *et al.* (Mol. and Cell. Bio., Mar. 1999, 1720-1730), Hanash S. (Nature Reviews, Applied Proteomics Collection, pp.9-14, March 2005)), and Hanash et al. (The Pharmacogenomics Journal, 3(6):308-311 (2003)) as support for its argument that mRNA expression cannot inevitably be correlated with levels of encoded protein. For the reasons discussed previously, and reiterated below, these cited references are not contrary to Applicants' asserted utility.

Haynes does not contradict the utility of the instant claims. Haynes is a review article dealing with the art of proteome analysis. The assertions in Haynes cited by the PTO were made in an effort to identify shortcomings in the art of mRNA quantification to argue for "proteome analysis to become an essential component in the comprehensive analysis of biological systems." Haynes, p. 1863. Haynes studied 80 selected samples from *Saccharomyces cerevisiae*, and reported "a general trend but no strong correlation between protein and transcript levels (Fig. 1)." Id. However, a cursory inspection of Fig. 1 shows a clear correlation between the mRNA levels and protein levels measured.

The 50-fold variation referred to by Haynes and cited by the PTO does not in any way show the absence of a correlation between mRNA and protein levels, but rather identifies the outer limits of variability in the authors' experiments. This variability may support the authors' assertion that the amount of a particular protein cannot accurately predict the particular level of the corresponding mRNA transcript, but it does not suggest an absence of a general correlation between mRNA and protein levels. Again, Applicants' utility is based on the differential expression of mRNA in rectal and lung tumor versus their normal tissue counterparts. Exact levels of expression are irrelevant. Moreover, Gygi states that the high degree of variability seen at low levels of mRNA (shown in inset of Fig. 1, Haynes p. 1863) is due to the fact that "the magnitude of the error in the measurement of mRNA levels is inversely proportional to the mRNA levels." Gygi, p. 1727. Considering that PRO180 mRNA has been shown in Example 18 of the specification to be more highly expressed in rectal tumors and normal lung than in normal

rectum and lung tumors, the variability identified by Haynes is even less applicable to establishing the absence of a correlation between mRNA and protein levels in the instant case.

Haynes studied whether there is a correlation between the level of mRNA expression and the level of protein expression for 80 selected genes from yeast. The genes were selected because they constituted a relatively homogeneous group with respect to predicted half-life and expression level of the protein products. *See* Haynes at 1863. Haynes did not examine whether a **change** in transcript level for a particular gene led to a **change** in the level of expression of the corresponding protein. Instead, Haynes determined whether the steady-state transcript level correlated with the steady-state level of the corresponding protein based on an analysis of 80 different genes.

Haynes reported to have "found a general trend but no strong correlation between protein and transcript levels." *Id.* However, a cursory inspection of Fig. 1 shows a clear correlation between the mRNA levels and protein levels measured. This correlation is confirmed by an inspection of the full-length research paper from which the data in Fig. 1 were derived, (Gygi *et al.*, Molecular and Cellular Biology, Mar. 1999, 1720-1730, previously submitted as Exhibit 2). Gygi states that "there was a general trend of increased protein levels resulting from increased mRNA levels," with a correlation coefficient of 0.935, indicating a strong correlation. Gygi at 1726. Moreover, Gygi also states that the correlation is especially strong for highly expressed mRNAs. *Id.* Thus, it is not clear that Haynes even supports the PTO's position, as Haynes did report a general trend, and Gygi reports a strong correlation between increasing mRNA levels and increasing protein levels.

The PTO focuses on the portion of Haynes where the authors reported that for some of the studied genes with equivalent mRNA levels, there were differences in corresponding protein expression, including some that varied by more than 50-fold. Similarly, Haynes reports that different proteins with similar expression levels were maintained by transcript levels that varied by as much as 40-fold. *Id.* Thus, Haynes showed that for one type of yeast, similar mRNA levels for *different* genes did not universally result in equivalent protein levels for the *different* gene products, and similar protein levels for *different* gene products did not universally result from equivalent mRNA levels for the *different* genes. These results are expected, since there are many factors that determine translation efficiency for a given transcript, or the half-life of the encoded protein. Not surprisingly, based on these results, Haynes concluded that protein levels

cannot always be accurately predicted from the level of the corresponding mRNA transcript *when looking at the level of transcripts across different genes.*

Importantly, Haynes did not say that for a single gene, the level of mRNA transcript is not positively correlated with the level of protein expression. Applicants have asserted that increasing or decreasing the level of mRNA for the same gene leads to an increase or decrease for the corresponding protein. Haynes did not study this issue and says absolutely nothing about it. Therefore, Haynes is not inconsistent with or contradictory to the utility of the instant claims, and offers no support for the PTO's position.

Gygi et al. is cited as stating "We found that the correlation between mRNA and protein levels was insufficient to predict protein expression levels from quantitative mRNA data. Indeed, for some genes, while the mRNA levels were of the same value the protein levels varied by more than 20-fold. Conversely, invariant steady-state levels of certain proteins were observed with respective mRNA transcript levels that varied by as much as 30-fold." Haynes et al. is cited as teaching that the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1).

Gygi states that "there was a general trend of increased protein levels resulting from increased mRNA levels," with a correlation coefficient of 0.935, indicating a strong correlation. Gygi, p. 1726. Moreover, Gygi also states that the correlation is especially strong for highly expressed mRNAs. Id. Considering that PRO180 mRNA has been shown in Example 18 of the specification to be more highly expressed in rectal tumors and normal lung than in normal rectum and lung tumors, Gygi actually provides strong evidence in support of a general correlation between mRNA and protein levels.

Applicants respectfully submit that Haynes and Gygi looked at static levels of mRNA across different genes, not changes in the level of expression for a single gene. Therefore, when Haynes and Gygi state that protein levels cannot be accurately predicted from the level of the corresponding mRNA, they are referring only to the static level of mRNA. Applicants have not asserted that protein levels can be predicted from static levels of mRNA, and the asserted utility does not depend on there being a correlation between static levels of mRNA and protein across different genes. Instead, Applicants have asserted that **changes** in mRNA level for an individual gene are generally correlated with **changes** in the level of the encoded protein. Applicants have asserted that because there is a change in the level of mRNA for PRO180 in lung and rectal

tumors compared to their normal tissue counterparts, the level of PRO180 protein will show a similar change. Predicting the absolute level of protein from the static level of mRNA is not required for this asserted utility since it is the change in the level of mRNA and protein that is important. Haynes and Gygi have absolutely no bearing on this issue since they examined static levels of mRNA for different genes.

The PTO also cites Chen *et al.* for support for the assertion that polypeptide levels cannot be accurately predicted from mRNA levels. In Chen, the authors examined the relationship between mRNA levels and protein levels in 76 lung adenocarcinomas and 9 non-tumor lung samples. Like Haynes, Chen examined the global relationship between mRNA and the corresponding protein abundance by calculating the average mRNA and protein level of all the samples for each gene or protein, and then looked for a correlation across different genes. As discussed above with respect to Haynes, this measurement of a correlation across genes is not relevant to Applicants' asserted utility. Chen also looked at the level of mRNA of 98 individual genes and their corresponding proteins across the samples. Chen reports that 21.4% (21 of 98) of the genes showed a statistically significant correlation between protein and mRNA expression.

Chen provides scant evidence to counter Applicants' asserted utility for the claimed antibodies because portions of Chen support Applicants' assertions, and the remaining portions provide little insight into the relationship between mRNA levels and corresponding protein levels for mRNA that is differentially expressed in tumor cells relative to normal cells. Rather than looking for mRNAs which were differentially expressed, Chen merely selected proteins whose identity could be determined regardless of any changes in expression level (Chen at 306, right column). Importantly, it is not known if there was any substantial difference in mRNA levels for the various genes across samples – in short, with the exception of the genes in Figures 2A-2C, it is not known if the genes examined were differentially expressed. Also of significance for Applicants' asserted utility is the fact that Chen did not attempt to examine any differential expression between the cancerous lung samples and the non-cancerous lung samples – Chen did not distinguish between cancer and normal samples in their analysis.

Applicants have asserted that changes in mRNA levels, particularly those which are two-fold or greater, will correspond with measurable changes in polypeptide expression. The data in Chen support Applicants' assertion. In Figures 2A-2C, Chen plots mRNA value vs. protein value for three genes. In these figures, a wide range of mRNA expression levels were observed

(approximately seven- to eight-fold), and a correlation between mRNA and protein levels was observed for all three mRNA/protein pairs. This supports Applicants' asserted correlation between changes in mRNA levels which are two-fold or greater and changes in polypeptide expression.

The PTO relies on the fact that Chen also reports a lack of correlation for some mRNA/protein pairs to support its assertion that polypeptide levels cannot be accurately predicted from mRNA levels. However, the lack of correlation reported by Chen could be a result of a lack of substantial changes in mRNA level. This can be understood by again turning to Figures 2A-2C. As noted above, where a wide range of mRNA expression levels are seen, a correlation between mRNA and protein levels was observed. However, if one examines the data points within a small range of mRNA levels for these same genes, e.g. 500-600 or 5000-6000 in Figs. 2A-2C, it is clear that a correlation would not be detected for the data within this range. This does not mean that a correlation between changes in mRNA and protein does not exist for these genes, as is evident when larger changes in mRNA expression are included in the analysis. Instead, this indicates that for relatively small changes in mRNA, any correlation is masked by imprecision in the measurements.

Chen's experiment compared mRNA levels vs. protein levels across samples without selecting mRNA that showed a difference in expression level. And unlike Applicants, Chen did not examine differences in mRNA between tumor and normal tissue. Since almost all samples tested by Chen were from the same type of tissue, few substantial variations in the level of mRNA or protein for a particular gene across the samples tested would be expected. Instead, it would be expected that most genes examined by Chen would have similar mRNA or protein levels across the samples. Figures 2A-2C of Chen demonstrate that the methods utilized by Chen cannot detect correlations between mRNA and protein levels when only small differences in mRNA expression are observed, but a correlation is detected when larger differences in mRNA expression are observed.

Accordingly, the only data reported by Chen which shows substantial changes in the expression of mRNA, Figures 2A-C, confirms Applicants' assertion that substantial changes in mRNA levels (e.g., 2-fold or greater) will correspond to substantial changes in polypeptide expression. Further, this data also explains the lack of observed correlation between mRNA levels and protein levels for other genes reported by Chen. Thus, even given Chen's inability to

detect a correlation between mRNA and protein in some genes, Chen's results do not refute Applicants' position.

Instead, Chen supports Applicants' position that a significant correlation between mRNA and protein levels exists for changes in mRNA levels that are 2-fold or greater. In further support of Applicants' position, Chen cites Celis *et al.* (FEBS Lett., 480:2-16 (2000)) stating that the authors "found a good correlation between transcript and protein levels among 40 well resolved, abundant proteins using a proteomic and microarray study of bladder cancer." *Chen* at 311, first column (emphasis added). As mentioned above, the lack of a correlation across genes is not relevant to Applicants' asserted utility, and therefore Chen's discussion of this issue and citation of Anderson and Seilhamer (Electrophoresis, 18:533-37 (1997)) and Gygi *et al.* (Mol. Cell. Bio., 19:1720-30 (1999)) offer no support for the PTO's position.

Even if the results in Chen supported the PTO's argument, which they do not as discussed above, one contrary example does not establish that one of skill in the art would find it is more likely than not there is no general correlation between changes in mRNA level and changes in protein level for an individual gene. There are other non-transcriptional mechanisms for regulating gene and protein expression (*i.e.*, post-transcriptional regulation of genes, translation efficiency, etc.). However, as shown by the declarations, references, and textbooks provided by Applicants, Applicants submit that the understanding in the art is that generally there is a correlation between a change in mRNA level and a change in protein level. In fact, the working hypothesis among those skilled in the art, as illustrated by the evidence presented by Applicants, is that there is a positive correlation between **changes** in mRNA levels and **changes** in protein levels for a particular gene.

The PTO cites Hanash S. as teaching that "There is a need to profile gene expression at the level of the proteome and to correlate changes in gene-expression profiles with changes in proteomic profiles. The two are not always linked-numerous alterations occur in protein levels that are not reflected at the RNA level." The PTO also cites Hanash et al. as teaching that "there is a need to assay protein levels and activities and numerous alterations may occur in proteins that are not reflected in changes at the mRNA level." These references also allegedly teach that "tumors are complex biological systems and no single type of molecular approach fully elucidates tumor behavior, necessitating analysis at multiple levels encompassing genomics and proteomics." According to the PTO, these references confirm that "it is not established in the art

that the accepted understanding or 'general rule' is that there is a direct correlation between mRNA levels and the level of expression of the encoded protein." Office Action at 10.

Applicants have already acknowledged that gene expression is regulated at numerous levels. However, the Declarations and supporting references supplied by Applicants make it clear that regulation of mRNA levels is the predominant mechanism of control for the majority of genes.

In support of the assertion that changes in mRNA are positively correlated to changes in protein levels, Applicants previously submitted a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Applicants also previously submitted a copy of the declaration of Paul Polakis, Ph.D., an expert in the field of cancer biology. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, **including the data discussed in paragraphs 4 and 5 above** [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion, based on over 20 years of scientific research, that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

The statements of Grimaldi and Polakis are supported by the teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) (previously submitted, herein after Cell 3rd) and (4th ed. 2002) (previously submitted, herein after Cell 4th)). Figure 9-2 of Cell 3rd shows the steps at which eukaryotic gene expression can be controlled. The first step depicted is transcriptional control. Cell 3rd provides that "[f]or most genes transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized." Cell 3rd at 403 (emphasis added). In addition, the text states that "Although controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made." Cell 3rd at 453 (emphasis added). Thus, as established in Cell 3rd, the predominant mechanism for regulating the amount of protein produced is by regulating transcription initiation.

In Cell 4th, Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*." Cell 4th at 302 (emphasis added). Similarly, Figure 6-90 on page 364 of Cell 4th illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Cell 4th at 364 (emphasis added). This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." Cell 4th at 379 (emphasis added).

Further support for Applicants' position can be found in the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)) (previously submitted) which states "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848 (emphasis added).

Additional support is also found in Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004, previously submitted. Zhigang studied the expression of prostate stem cell antigen (PSCA) protein and mRNA to validate it as a potential molecular target for diagnosis and

treatment of human prostate cancer. The data showed "a high degree of correlation between PSCA protein and mRNA expression" Zhigang at 4. Of the samples tested, 81 out of 87 showed a high degree of correlation between mRNA expression and protein expression. The authors conclude that "it is demonstrated that PSCA protein and mRNA overexpressed in human prostate cancer, and that the increased protein level of PSCA was resulted from the upregulated transcription of its mRNA." Zhigang at 6. Even though the correlation between mRNA expression and protein expression occurred in 93% of the samples tested, not 100%, the authors state that "PSCA may be a promising molecular marker for the clinical prognosis of human Pca and a valuable target for diagnosis and therapy of this tumor." *Id.* at 7

Further, Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002), previously submitted, states the following:

> The **fundamental principle** of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells...[M]ost efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Meric *et al.* at 971 (emphasis added).

Those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression.

The PTO asserts that the Declarations of Mr. Grimaldi and Dr. Polakis were not persuasive. According to the PTO, Alberts and Lewin actually support the position that further research would have to be carried out to determine if the polypeptide expression levels track with the expression levels of the corresponding mRNA. In particular, the PTO asserts that Alberts and Lewin show that there are several levels that control gene expression both at the transcriptional (i.e., mRNA synthesis) and the translational (i.e., protein production) levels. The PTO maintains that one skilled in the art would not accept that increased mRNA levels directly correlate with the level of the corresponding polypeptide in view of the multitude of controls at the transcriptional and translational levels.

These arguments are not responsive. Applicants have already acknowledged that gene expression is regulated at numerous levels. However, as the supporting references and declarations Applicants have supplied make clear, regulation of mRNA levels is the predominant mechanism of control for the majority of genes.

The PTO also asserts that, while Zhigang et al. does show protein expression, the experiments were carried out to demonstrate this. Thus, the PTO maintains that Zhigang demonstrates that one needs to actually determine the expression of the protein to be sure of expression. As previously noted, Zhigang reported that the correlation between mRNA expression and protein expression occurred in 93% of the samples tested. This was considered by the authors to be a high degree of correlation between protein and mRNA expression. Accordingly, Applicants maintain that Zhigang is consistent with Applicants' position that, in general, differential mRNA expression leads to differential expression of the encoded polypeptide, and that one of skill in the art would expect to see, more likely than not, a correlation between mRNA and protein expression.

The PTO asserts that Applicants have taken the statements by Meric out of context. According to the PTO, Meric indicates most efforts have concentrated on gene expression at the mRNA level due to the advent of cDNA array technology, which facilitated this type of analysis. The PTO asserts that Meric et al., in agreement with Alberts and Lewin, acknowledges that gene expression is quite complicated and is regulated at the level of mRNA stability, mRNA translation and protein stability and that Meric et al. goes on to indicate that the components of the translation machinery and signal pathways involved in the activation of translation initiation represent good targets for cancer therapy (Office Action at 7). The PTO argues that, if it was the accepted understanding in the art that there is a direct correlation between mRNA levels and the level of expression of the encoded polypeptide, there would not be a need to target the translational machinery, unless of course the two are regulated separately.

As noted above, Applicants have already acknowledged that gene expression is regulated at numerous levels. However, as the supporting references and Declarations Applicants have supplied make clear, regulation of mRNA levels is the predominant mechanism of control for the majority of genes. Meric supports this assertion because "[t]he **fundamental principle** of molecular therapeutics in cancer is to exploit the **differences** in gene expression between cancer cells and normal cells." Meric *et al.* at 971 (emphasis added). The only reason mRNA is of any interest in studying the mechanism of cancer formation and growth is because mRNA encodes protein. If there were no general correlation between differences in mRNA and differences in protein, there would be no reason to study changes in mRNA. Furthermore, with respect to the PTO's argument that there would be no need to target translational machinery for cancer therapy

if there was a direct correlation between mRNA and protein, Applicants maintain that any point in the process of producing a polypeptide involved in cancer may be exploited as a target for therapy. The inclusion of translational machinery amongst the many potential target points does not indicate in any way that there is no correlation between mRNA levels and polypeptide levels.

Applicants again submit that a lack of known role for PRO180 in cancer does not prevent its use as a diagnostic tool for cancer. Whether the differential expression of PRO180 is a cause or result of the rectal or lung tumors is irrelevant to whether its differential expression can be used to assist in diagnosis of cancer – one does not need to know why PRO180 is differentially expressed, or what the consequence of the differential expression is, in order to exploit the differential expression to distinguish tumor from normal tissue. In fact the Revised Interim Utility Guidelines promulgated by the PTO recognize that proteins which are differentially expressed in cancer have utility. (*See* the caveat in Example 12 which state that the utility requirement is satisfied where a protein is expressed in melanoma cells but not on normal skin and antibodies against the protein can be used to diagnose cancer.)

In summary, Applicants submit that they have offered sufficient evidence to establish that it is more likely than not that one of skill in the art would believe that because the PRO180 mRNA is differentially expressed in lung and rectal tumors, the PRO180 polypeptide will also be differentially expressed in lung and rectal tumors. This differential expression of the PRO180 polypeptide makes it useful as a diagnostic tool for cancer, particularly lung and rectal cancer.

The Arguments made by the PTO are Not Sufficient to satisfy the PTO's Initial Burden of Offering Evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility"

As stated above, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

Applicants remind the PTO that the M.P.E.P. cautions that rejections for lack of utility are rarely sustained by federal courts, and that generally speaking, a utility rejection was sustained because the applicant asserted a utility "that could **only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art.**" M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (underline emphasis in original, bold emphasis added). Rather than being wholly inconsistent with contemporary knowledge in the art, Applicants' asserted utility is squarely within the teaching of leading textbooks in the field, and is supported by references and the declarations of skilled experts.

The PTO has failed to offer any arguments or cite any references to establish "that one of ordinary skill in the art would reasonably doubt" that polypeptides differentially expressed in certain tumors can be used as a diagnostic tool. The cited references do not support the PTO's position and are not contrary to Applicants' asserted utility. Likewise, the PTO has not offered any substantial arguments or evidence to rebut the numerous declarations and references Applicants' have submitted in support of their asserted utility. Given the lack of support for the PTO's position, Applicants submit that the PTO has not met its initial burden of overcoming the presumption that the asserted utility is sufficient to satisfy the utility requirement. And even if the PTO has met that burden, the Applicants' supporting rebuttal evidence is sufficient to establish that one of skill in the art would be more likely than not to believe that the claimed polypeptides can be used as diagnostic tools for cancer, particularly lung and rectal cancer.

Specific Utility

The Asserted Substantial Utilities are Specific to the Claimed Polypeptides

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO180 gene in certain types of cancer cells, along with the declarations and references discussed above, provide a specific utility for the claimed polypeptides.

As discussed above, there are significant data which show that the gene encoding the PRO180 polypeptide is expressed at least two-fold higher in rectal tumor and normal lung tissue compared to normal rectum and lung tumor, respectively. Applicants have also established that the general understanding in the field is that there is a correlation between gene expression and protein expression. Thus, Applicants have provided strong evidence that the PRO180 gene and polypeptide are associated with rectal and lung tumors. Contrary to the assertions of the PTO, Applicants submit that they have provided sufficient evidence associating the PRO180 gene and polypeptide with a specific disease. The asserted utility as a diagnostic tool for cancer, particularly rectal and lung tumor, is a specific utility – it is not a general utility that would apply to the broad class of polypeptides.

Conclusion

The PTO has asserted three arguments for why there is a lack of a substantial utility: (1) there is no data showing differential expression of the PRO180 polypeptide in certain tumors; (2) the literature demonstrates that gene expression and protein expression do not always correlate; and, (3) because there is no clear, reasonable correlation between gene expression and protein expression, the claimed polypeptides cannot be used as cancer diagnostic or therapeutic tools. Applicants have addressed each of these arguments in turn.

First, the Applicants provide a declaration stating that the data in Example 18 reporting higher expression of the PRO180 gene in rectal tumor and normal lung tissue compared to normal rectal and lung tumor tissue, are real and significant.

Second, Applicants submit that excerpts from leading textbooks in the field, supported by the second Grimaldi Declaration and the Polakis Declaration and the references discussed above, demonstrate that it is well-established in the art that a change in mRNA levels *generally*

correlates to a corresponding change in the encoded protein levels. One of skill in the art will recognize that polypeptides differentially expressed in certain cancers have utility as diagnostic tools for cancer.

Third, Applicants have shown that the references relied on by the PTO do not support the PTO's position that one of skill in the art would reasonably doubt the asserted utility.

Finally, Applicants have pointed out that the substantial utilities described above are specific to the claimed polypeptides because the PRO180 gene and polypeptide are differentially expressed in certain cancer cells compared to the corresponding normal cells. This is not a general utility that would apply to the broad class of polypeptides.

Given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed polypeptides as diagnostic tools. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants remind the PTO that:

> A small degree of utility is sufficient . . . The claimed invention must only be capable of performing **some** beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely... A commercially successful product is not required... Nor is it essential that the invention accomplish all its intended functions... or operate under all conditions... partial success being sufficient to demonstrate patentable utility... In short, **the defense of non-utility cannot be sustained without proof of total incapacity**. If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed polypeptides relating to PRO180 set forth in the specification. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejection under 35 U.S.C. §112 – Enablement

The PTO has maintained its rejection of Claims 42-51, and rejects newly added Claims 52-55 under 35 U.S.C. § 112, first paragraph. The PTO states that since the claimed invention is

not supported by either a specific asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention.

Applicants submit that in the discussion of the rejection under 35 U.S.C. § 101 above, Applicants have established a substantial, specific, and credible utility for the claimed polypeptides. Applicants therefore respectfully request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. §112, first paragraph.

In addition, the PTO maintains the rejection of Claims 42-43 and 50-51, and newly rejects claims 52-55, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. According to the PTO, "the specification does disclose any polypeptide variant that is at least 95% identical to SEQ ID NO:2, and is differentially expressed in rectal and lung tumors and one of skill in the art would not know if such a polypeptide even exists." Office Action at 15.

The pending claims are to polypeptides that have at least 95% or 99% amino acid sequence identity to the recited sequence and are "more highly expressed in rectal tumors or normal lung compared to normal rectum or lung tumor respectively, or wherein said isolated polypeptide is encoded by a polynucleotide that is more highly expressed in expressed in rectal tumors or normal lung compared to normal rectum or lung tumor respectively" or the "isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:2 in rectal or lung tissue samples."

Applicants submit that the claimed polypeptides are enabled, as one of skill in the art would know how to make and use them. It is well-established in the art how to make the claimed polypeptides which have at least 95% or 99% amino acid sequence identity to the disclosed sequences related to SEQ ID NO:2. Applicants have disclosed how to determine if the claimed polypeptides or encoding nucleic acids are differentially expressed in rectal tumors or normal lung compared to normal rectum or lung tumor. Applicants have also disclosed how to make antibodies to the polypeptide of SEQ ID NO:2, and given the high amino acid sequence homology of the claimed polypeptides, one of skill in the art would know how to make antibodies to SEQ ID NO:2 from the claimed polypeptides. Thus, one of skill in the art would know how to make the claimed polypeptides.

As discussed above, Applicants submit that they have established that one of skill in the art would believe that it is more likely than not that the PRO180 gene and polypeptide are

differentially expressed in rectal and lung tumors such that they can be used as cancer diagnostic tools. Given the disclosure in the specification and the level of skill in the art, a skilled artisan would know how to use the claimed polypeptides as diagnostic tools. For example, polypeptides which have at least 95% or 99% amino acid sequence identity to the disclosed sequences and are "more highly expressed in rectal tumors or normal lung compared to normal rectum or lung tumor respectively..." can be used as diagnostic tools since the claimed polypeptides or their encoding nucleic acids are differentially expressed in rectal and lung tumors. Other claimed polypeptides which have at least 95% or 99% amino acid sequence identity to the disclosed sequences and "said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:2 in rectal and lung tissue samples," are also useful diagnostic tools. Because the polypeptide of SEQ ID NO:2 is more likely than not likely differentially expressed in rectal and lung tumors, antibodies for specific detection of this polypeptide in rectal and lung tissue samples are useful diagnostic tools.

Given the skill in the art and the disclosure of how to make and use the claimed polypeptides, Applicants request that the PTO reconsider and withdraw its rejection under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. §112 – Written Description

The PTO has maintained its rejection of Claims 42-43 and rejects new Claims 52-55 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. The PTO maintains that the presently claimed polypeptides have not been associated with any particular biological activity or function coupled with the disclosed structure, and that the claimed polypeptides may have functions and structures that differ greatly from that of PRO180. Further, the PTO states that one of skill in the art would not be able to identify the encompassed molecules as being identical to those claimed.

The Legal Standard for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph is whether the disclosure "reasonably conveys to

artisan that the inventor had possession at that time of the later claimed subject matter." *In re Kaslow*, 707 F.2d 1366, 1375, 2121 USPQ 1089, 1096 (Fed. Cir. 1983); *see also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. *See e.g., Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil v. Atlantic Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000).

The Current Invention is Adequately Described

As noted above, whether the Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teaching provided by the specification. The inventor is not required to describe every single detail of his/her invention. An Applicant's disclosure obligation varies according to the art to which the invention pertains. The present invention pertains to the field of recombinant DNA/protein technology. It is well-established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the invention was made.

The pending claims are related to isolated polypeptides having at least 95% or 99% amino acid sequence identity to several polypeptides related to SEQ ID NO:180, and satisfy the limitation "wherein said isolated polypeptide is more highly expressed in rectal tumors or normal lung compared to normal rectum or lung tumor respectively, or wherein said isolated polypeptide is encoded by a polynucleotide that is more highly expressed in rectal tumors or normal lung compared to normal rectum or lung tumor respectively" or "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:2 in rectal or lung tissue samples."

Applicants maintain that there is no substantial variation within the species which fall within the scope of the amended claims, which require at least 95% or 99% amino acid sequence identity to the disclosed sequences related to SEQ ID NO:2. Applicants note that the pending

Claims are analogous to the claims discussed in Example 14 of the written description training materials. In Example 14, the written description requirement was found to be satisfied for claims relating to polypeptides having 95% homology to a particular sequence and possessing a particular catalytic activity, even though the applicant had not made any variants. Similarly, the pending claims also have very high sequence homology to the disclosed sequences and must share the same expression pattern in certain tumors, or share an epitope sufficient to generate antibodies which specifically detect the polypeptide of SEQ ID NO:2 in rectal or lung tissue samples.

In Example 14, the procedures for making variants were known in the art and the disclosure taught how to test for the claimed catalytic activity. Similarly, in the instant application, it is well known in the art how to make polypeptides with at least 95% amino acid sequence identity to the disclosed sequences. In addition, the specification discloses how to test to determine if the polypeptide or encoding nucleic acid is differentially expressed in rectal or lung tumors, and how to make antibodies which specifically detect the polypeptide of SEQ ID NO:2 in rectal or lung tissue samples. Like Example 14, the genus of polypeptides that have at least 95% or 99% amino acid sequence identity to the disclosed sequences will not have substantial variation.

The PTO has responded to these arguments by stating that the claimed polypeptides have not been associated with any particular biological activity or function coupled with the disclosed structure, and that the claimed polypeptides may have functions and structures that differ greatly from that of PRO180. Further, the PTO states that one of skill in the art would not be able to identify the encompassed molecules as being identical to those claimed. Further, the PTO states that specification does not disclose any polypeptide that is 95% or 99% identical to SEQ ID NO:2 and is over-expressed in rectum tumor and normal lung relative to normal rectum and lung tumor respectively.

In a recent Federal Circuit decision, *In re Wallach*, 378 F.3d 1330, 1333-34 (Fed. Cir. 2004), the Court stated:

> [W]e agree with Appellants that the state of the art has developed such that the complete amino acid sequence of a protein may put one in possession of the genus of DNA sequences encoding it, and that one of ordinary skill in the art at the time the '129 application was filed may have therefore been in possession of the entire genus of DNA sequences that can encode the disclosed partial protein sequence, even if individual species within that genus might not have been described or

> rendered obvious. ... A claim to the genus of DNA molecules complementary to the RNA having the sequences encompassed by that formula, even if defined only in terms of the protein sequence that the DNA molecules encode, while containing a large number of species, is definite in scope and provides the public notice required of patent applicants.
>
> ***
>
> Moreover, we see no reason to require a patent applicant to list every possible permutation of the nucleic acid sequences that can encode a particular protein for which the amino acid sequence is disclosed, given the fact that it is, as explained above, a routine matter to convert back and forth between an amino acid sequence and the sequences of the nucleic acid molecules that can encode it. *Id.* (emphasis added).

The Court did not require the Applicants in *Wallach* to actually make and individually describe all of the vast number of sequences which encode the disclosed sequence. This is in spite of the fact that there is no possibility that even the most skilled artisan could "envision the detailed chemical structure of all or a significant number" of encompassed polynucleotides. Because it is routine to convert between amino acid sequences to nucleic acid sequences, disclosure of a single amino acid sequence was sufficient to describe the very large genus of nucleic acids which could encode the sequence.

The facts in *Wallach* are very similar to the instant case. Here, Applicants have disclosed SEQ ID NO:2, and claim polypeptides which are homologous to it and have the functional limitation of differential expression or the ability to generate antibodies which can be used to specifically detect SEQ ID NO:2 in lung or rectum tissue samples. It is routine in the art to create polypeptides which have at least 95% or 99% sequence identity to SEQ ID NO:2 – it is just as predictable and easy as creating all of the nucleic acids which encode a particular amino acid sequence. Similarly, it is well within the skill of those in the art to determine which polypeptides share the requisite expression patterns or can be used to make the recited antibodies. These structure/function combinations are sufficient to describe the claimed polypeptides. The *Wallach* opinion makes clear that there is no need to list each individual sequence within the genus to adequately describe the genus.

In conclusion, Applicants submit that they have satisfied the written description requirement for the pending claims based on the actual reduction to practice of SEQ ID NO:2, by specifying a high level of amino acid sequence identity, by describing how to test for differential

expression of the polypeptide and encoding nucleic acid, and by describing how to make antibodies to the disclosed sequence, all of which result in a lack of substantial variability in the species falling within the scope of the instant claims. Applicants submit that this disclosure would allow one of skill in the art to "recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus." Hence, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

New Rejections under 35 U.S.C. §112

Claims 42-44, 46-48 and 50-55 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite. Claims 42-44, 47-48 and 50-55 are indefinite in view of the limitations that the claimed protein lacks its associated signal peptide or comprises an "extracellular domain" optionally lacking its associated signal peptide. According to the PTO, these limitations are indefinite because neither the figure (Figure 2) nor the specification define or teach the metes and bounds of the extracellular domain.

The features described in Figure 2 for SEQ ID NO:2 indicate that there are transmembrane domains at amino acids 13-33, 54-73, 94-113, 122-141 and 160-180 and myristoylation sites at amino acids 57-63, 95-101, 99-105, 124-130 and 183-189. Accordingly, the extracellular domains lie at amino acids 34-53, 114-121, and 181-266. Applicants have amended the claims to provide the locations of the extracellular domains.

Claims 42-44, 46, 48, and 50-55 are rejected under 35 U.S.C. § 112, second paragraph as indefinite for reciting a "signal peptide." The claims have been amended to remove any reference to a signal peptide.

Claims 42-44, 47-48 and 50-55 are rejected under 35 U.S.C. § 112, first paragraph, because the amendments allegedly introduce new matter into the claims. The PTO asserts that Figure 2 does not disclose the extracellular domain as being amino acids 34-366, and that there is no disclosure of any nucleic acid or polypeptide that is at least 95% identical to SEQ ID NO:2 that is overexpressed in rectum tumor or normal lung compared to normal lung or rectum tumor.

For the reasons provided in the above discussion regarding the written description requirement and the extracellular domains, Applicants maintain that the specification adequately describes the claimed polypeptides. Accordingly, the claims do not contain new matter.

Priority

Priority is granted to PCT/US00/23328, filed 24 August 2000, as the disclosure of this PCT application is identical to the instant disclosure. However, the Examiner did not grant priority to PCT/US00/08439, USSN 09/380,137, PCT/US99/12252 and 60/096,102 on the assertion that these applications do not disclose the microarray assay upon which applicant relies for utility of the instantly claimed polypeptides.

As an initial matter, Applicants would like to clarify that Example 18 used quantitative PCR analysis of a cDNA library to measure mRNA expression, not a microarray analysis. With respect to the priority date of the present application, Applicants maintain that this application is entitled to priority to the previously cited applications, including U.S. Provisional Application 60/096,102 filed August 10, 1998.

Rejections under 35 U.S.C. §102(b) – Feng et al.

The PTO rejects Claims 42-55 as anticipated under 35 U.S.C. § 102(b) by Feng et al (WO 99/24836, published May 1999).

Applicants are entitled to priority to U.S. Provisional Application No. 60/096,012 filed on **August 10, 1998**. This application includes the disclosure of the full length sequence of SEQ ID NOS:1 and 2. As explained more fully below, Applicants demonstrated, by means of the disclosure in their provisional application filed August 10, 1998, that they were in possession of so much of the claimed invention, i.e. SEQ ID NO:2, as disclosed in the Feng et al. reference dated May 1999. As stated by the PTO, "a chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present." Office Action at 21. Applying this reasoning, Applicants provided the chemical composition of SEQ ID NO:2 as of August 10, 1998. They necessarily therefore also provided the properties of SEQ ID NO:2 as of August 10, 1998. The Feng et al. reference, published May 1999, cannot therefore anticipate the claimed invention.

Further, the well-established "Stempel Doctrine" stands for the proposition that a patent applicant can effectively swear back of and remove a cited prior art reference by showing that he or she made that portion of the claimed invention that is disclosed in the prior art reference. (*In re Stempel*, 113 USPQ 77 (CCPA 1957)). In other words, a patent applicant need not

demonstrate that he or she made the entire claimed invention in order to remove a cited prior art reference. He or she need only demonstrate prior possession of that portion of his or her claimed invention that is disclosed in the prior art reference and nothing more.

The Stempel Doctrine was extended to cases where a reference disclosed the claimed compound but failed to disclose a sufficient utility for it in *In re Moore*, 170 USPQ 260 (CCPA 1971). More specifically, the patent applicant (Moore) claimed a specific chemical compound called PFDC. In support of a rejection of the claim under 35 U.S.C. § 102, the Examiner cited a reference which disclosed the claimed PFDC compound, but did not disclose a utility for that compound. Applicant Moore filed a declaration under 37 C.F.R. § 1.131 demonstrating that he had made the PFDC compound before the effective date of the cited prior art reference, even though he had not yet established a utility for that compound. The lower court found the 131 declaration ineffective to swear back of and remove the cited reference, reasoning that since Moore had not established a utility for the PFDC compound prior to the effective date of the cited prior art reference, he had not yet completed his "invention".

On appeal, however, the CCPA reversed the lower court decision and indicated that the 131 declaration filed by Moore was sufficient to remove the cited reference. The CCPA relied on the established Stempel Doctrine to support its decision, stating:

> An applicant need **not** be required to show [in a declaration under 37 C.F.R. § 1.131] any more acts with regard to the subject matter claimed that can be carried out by one of ordinary skill in the pertinent art following the description contained in the reference....the determination of a practical utility when one is not obvious need **not** have been accomplished prior to the date of a reference unless the reference also teaches how to use the compound it describes. (Id. at 267, emphasis added).

Thus, *In re Moore* confirms the Stempel Doctrine, holding that in order to effectively remove a cited reference with a declaration under 37 C.F.R. § 1.131, an applicant need only show that portion of his or her claimed invention that appears in the cited reference. Moreover, *In re Moore* stands for the proposition that when a cited reference discloses a claimed chemical compound either absent a utility or with a utility that is different from the one appearing in the claims at issue, a patent applicant can effectively swear back of that reference by simply showing prior possession of the claimed chemical compound. In other words, under this scenario, the

patent applicant need not demonstrate that he or she had discovered a patentable utility for the claimed chemical compound prior to the effective date of the prior art reference.

While these cases discuss the ability to effectively swear back of the cited reference by way of a 131 declaration, Applicants submit that the same reasoning applies here, where the application claims priority back to a disclosure that predates the cited references. Applicants demonstrated, by means of the disclosure in their provisional application filed August 10, 1998, that they were in possession of so much of the claimed invention, i.e. SEQ ID NO:2, as disclosed in the Feng et al. reference dated May 1999. Thus, Applicants respectfully submit that the cited reference is not available as prior art, and request that the rejection under 35 USC §102 be removed.

In addition, Applicants maintain that the Declaration under 37 CFR §1.131, which was previously submitted on December 9, 2004, establishes that the presently claimed invention antedates the Feng et al. reference. The Declaration and the supporting evidence submitted therewith established conception of the invention prior to the May 1999 publication date of Feng et al., and diligent reduction to practice thereafter. Withdrawal of the rejection under 35 U.S.C. § 102 is therefore respectfully requested.

Rejection under 35 U.S.C. §102(a) – Baker et al.

The PTO has rejected Claims 42-55 as being anticipated by Baker et al. (WO 99/63088, published 12/99). The Examiner states that because the present application is entitled only to a priority date of August 24, 2000, the Baker reference is being reapplied.

Applicants maintain that the Declaration under 37 CFR §1.131, which was previously submitted on January 28, 2004, establishes that the presently claimed invention antedates the Baker et al. reference. The Declaration and the supporting evidence submitted therewith established conception of the invention prior to the 12/99 publication date of Baker et al., and diligent reduction to practice thereafter. Withdrawal of the rejection under 35 U.S.C. § 102(a) is therefore respectfully requested.

CONCLUSION

In view of the above, Applicants respectfully maintain that the claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: Dec. 5, 2005

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